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WO 01/05425 A2

(54) Title: COMBINED PREPARATIONS COMPRISING ANTITUMOR AGENTS

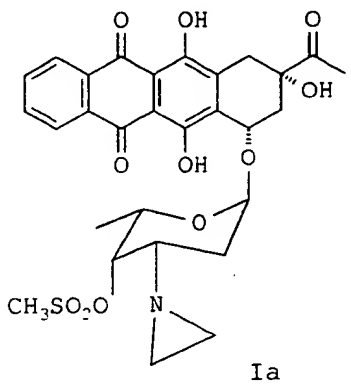
(57) Abstract: There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis.

Title: "Combined preparations comprising antitumor agents"

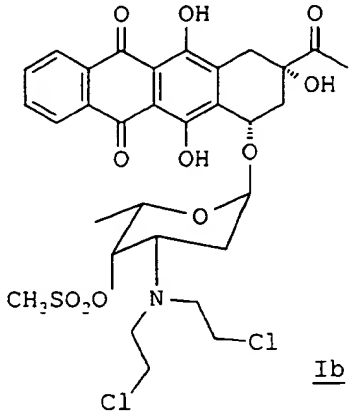
The present invention pertains to the field of neoplastic disease therapy. Particularly, this invention provides an antitumor composition comprising an alkylating anthracycline and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody (rhuMab) anti-HER2, trastuzumab (Herceptin™), having a synergistic or additive antineoplastic effect.

The present invention provides, in a first aspect, a pharmaceutical composition for use in antineoplastic therapy in mammals, including humans, comprising

- an alkylating anthracycline of formula Ia or Ib



Ia



Ib

- a recombinant humanized anti-HER2 antibody and a pharmaceutically acceptable carrier or excipient.

The recombinant humanized anti-HER2 antibody is preferably, the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

The chemical names of the alkylating anthracyclines of formula Ia and Ib are 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin (Ia) and 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin (Ib). These alkylating anthracyclines were described in Anticancer Drug Design (1995), vol. 10, 641-653, and claimed respectively in US-A-5,532,218 and US-A-5,496,800. Both compounds intercalate

into DNA via the chromophore and alkylate guanine at N^7 position in DNA minor groove via their reactive moiety on position 3' of the amino sugar. Compounds Ia and Ib are able to circumvent the resistance to all major classes of cytotoxics, indicating that the compounds represent a new class of cytotoxic antitumor drugs.

The recombinant humanized monoclonal antibody anti-HER2 trastuzumab (Herceptin™) is described in various scientific publications, for example Cancer Res., 1998, 58:2825-2831.

The present invention also provides a product comprising an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, as combined preparation for simultaneous, separate or sequential use in antitumor therapy.

A further aspect of the present invention is to provide a method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

A still further aspect of the present invention is to provide a method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, preferably the the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, in amounts effective to produce a synergistic antineoplastic effect.

By the term "a synergistic antineoplastic effect" as used herein is meant the inhibition of the growth tumor, preferably

the complete regression of the tumor, administering an effective amount of the combination of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody to mammals, including humans.

By the term "administered" or "administering" as used herein is meant any acceptable manner of administering a drug to a patient which is medically acceptable including parenteral and oral administration. By "parenteral" is meant intravenous, subcutaneous and intramuscular administration. Oral administration includes administering the costituents of the combined preparation in a suitable oral form such as, e.g., tablets, capsules, suspensions, solutions, emulsions, powders, syrups and the like. Parenteral administration includes administering the costituents of the combined preparation by subcutaneous, intravenous or intramuscular injections.

The actual preferred method and order of administration of the combined preparations of the invention may vary according to, inter alia, the particular pharmaceutical formulation of the alkylating anthracycline of formula Ia or Ib as defined above being utilized, the particular pharmaceutical formulation of the recombinant humanized anti-HER2 antibody being utilized, the particular cancer being treated, and the particular patient being treated.

The dosage ranges for the administration of the combined preparation may vary with the age, condition, sex and extent of the disease in the patient and can be determined by one of skill in the art.

The dosage regimen must therefore be tailored to the particular of the patient's conditions, response and associate treatments in a manner which is conventional for any therapy, and may need to be adjusted in response to changes in conditions and/or in light of other clinical conditions.

In the method of the subject invention, the alkylating anthracycline may be administered simultaneously with the

recombinant humanized anti-HER2 antibody, or the compounds may be administered sequentially, in either order.

In the method of the subject invention, for the administration of the alkylating anthracycline of formula Ia or Ib as defined above, the course of therapy generally employed is from about 0.1 to about 200 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 1 to about 50 mg/m^2 of body surface area.

In the method of the subject invention, for the administration of the recombinant humanized anti-HER2 antibody, for example for the administration of the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, the course of therapy generally employed is from about 1 to about 1000 mg/m^2 of body surface area. More preferably, the course therapy employed is from about 50 to about 500 mg/m^2 of body surface area.

The antineoplastic therapy of the present invention is, in particular, suitable for treating breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors in mammals, including humans. More in particular, the combined use of an alkylating anthracycline according to the invention and a recombinant humanized anti-HER2 antibody, for example the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, can be suitable for the treatment of patients with cancers over-expressing the HER2 protein, for example, for patient with metastatic breast cancer over-expressing the HER2 protein.

The antineoplastic therapy according to this invention also comprises the prevention and/or treatment of tumor metastasis.

A still further aspect of the present invention is the use of an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, preferably the recombinant humanized monoclonal antibody anti-HER2 trastuzumab, for the treatment of tumors by angiogenesis inhibition.

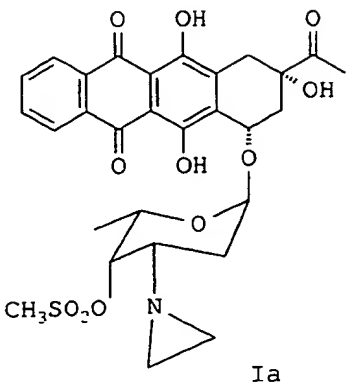
As stated above, the effectiveness of an alkylating anthracycline of formula Ia or Ib and a recombinant humanized anti-HER2 antibody is significantly increased without a parallel increased toxicity. In other words, the combined therapy of the present invention enhances the antitumoral effects of the alkylating anthracycline of formula Ia or Ib as defined above and of a recombinant humanized anti-HER2 antibody and thus yields the most effective and least toxic treatment for tumors.

The synergistic action displayed by the combined preparations according to the present invention can be shown, for instance, by testing the activity of the combination in mice bearing human tumor xenografts overexpressing HER2 protein, following, for example, the method described in Cancer Research, 1998, 58:2825-2831.

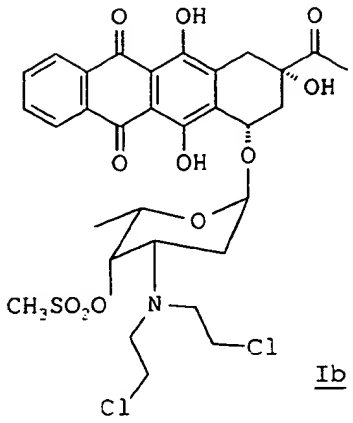
Suitable modifications and adaptations of a variety of conditions and parameters normally encountered in clinical therapy which are obvious to those skilled in the art are within the scope of this invention.

CLAIMS

1. Products containing an alkylating anthracycline of formula Ia or Ib:



Ia



Ib

and a recombinant humanized anti-HER2 antibody as a combined preparation for simultaneous, separate or sequential use in antitumor therapy.

2. Products according to claim 1, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

3. Products according to claim 1 or 2, wherein the alkylating anthracycline is 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin.

4. Products according to any one of claims 1 to 3, wherein the antitumor therapy is for treating cancers over-expressing HER2 protein.

5. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient, an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody.

6. A pharmaceutical composition according to claim 5 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

7. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the treatment of tumors, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

8. Use according to claim 7 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

9. Use of an alkylating anthracycline of formula Ia or Ib as defined in claim 1 and a recombinant humanized anti-HER2 antibody in the preparation of a medicament for use in the prevention and/or treatment of tumor metastasis, wherein the alkylating anthracycline and the recombinant humanized anti-HER2 antibody are administered simultaneously, separately or sequentially.

10. Use according to claim 9 wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

11. A method of treating a mammal, including a human, suffering from a neoplastic disease comprising administering to said mammal an alkylating anthracycline of formula Ia or Ib as defined above and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

12. A method according to claim 11, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

13. A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent in a mammal, including a human, in need thereof, the method comprising administering to said mammal a combined preparation comprising an alkylating anthracycline of formula Ia or Ib as defined above, and a recombinant humanized anti-HER2 antibody, in amounts effective to produce a synergistic antineoplastic effect.

14. A method according to claim 13, wherein the recombinant humanized anti-HER2 antibody is the recombinant humanized monoclonal antibody anti-HER2 trastuzumab.

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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN S.P.A.** [IT/IT]; Via Robert Koch, 1.2, I-20152 Milano (IT).

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(75) Inventors/Applicants *(for US only)*: **GERONI, Cristina** [IT/IT]; Via Correggio, 48, I-20149 Milan (IT). **RIPAMONTI, Marina** [IT/IT]; Viale Fulvio Testi, 91, I-20162 Milan (IT). **CARUSO, Michele** [IT/IT]; Via Desiderio, 3, I-20131 Milan (IT). **SUARATO, Antonino** [IT/IT]; Via degli Imbriani, 39, I-20100 Milano (IT).

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(54) Title: COMBINED PREPARATIONS COMPRISING DAUNORUBICIN DERIVATIVES AND HER2 ANTIBODIES

(57) Abstract: There are provided the combined use of 4-demethoxy-3'-deamino-3'-aziridinyl-4'-methansulfonyl daunorubicin or 4-demethoxy-N,N-bis(2-chloroethyl)-4'-methansulfonyl daunorubicin and a recombinant humanized anti-HER2 antibody, preferably trastuzumab, in the treatment of tumors and the use of said combination in the treatment and/or prevention of tumor metastasis.

INTERNATIONAL SEARCH REPORT

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According to International Patent Classification (IPC) or to both national classification and IPC

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BASELGA J ET AL: "HER2 Overexpression and Paclitaxel sensitivity in breast cancer: Therapeutic implications" ONCOLOGY,CH,S. KARGER AG, BASEL, vol. 11, no. 3, SUPPL. 02, March 1997 (1997-03), pages 43-48, XP002100077 ISSN: 0030-2414 abstract page 46, column 2, paragraph 4 -page 47, column 1 ---	1-14
Y	US 5 677 171 A (SHEPARD H MICHAEL ET AL) 14 October 1997 (1997-10-14) claims 18,19,37,39 --- -/--	1-14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gonzalez Ramon, N

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INTERNATIONAL SEARCH REPORT

Intern ial Application No
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